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[REDACTED] EXAMINER

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[REDACTED] ART UNIT [REDACTED] PAPER NUMBER

1637

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*2/26*

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

09/530,746

Applicant(s)

KESSLER ET AL.

Examiner

Teresa E Strzelecka

Art Unit

1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) Responsive to communication(s) filed on 27 November 2002.
- 2a) This action is FINAL.                  2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) Claim(s) 1-25 is/are pending in the application.
- 4a) Of the above claim(s) 16-25 is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 1-15 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

- 11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

### Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some \* c) None of:
1. Certified copies of the priority documents have been received.
  2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

### Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) 12, 24
- 4) Interview Summary (PTO-413) Paper No(s) \_\_\_\_\_
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other \_\_\_\_\_

## **DETAILED ACTION**

### ***Election/Restrictions***

1. Applicant's election without traverse of Group I (claims 1-15) in Paper No. 23 is acknowledged.
2. Claims 16-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 23.
3. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

### ***Specification***

4. The disclosure is objected to because of the following informalities:
  - A) On page 3, line 2 "... sensitivity in the ag range... ". It is not clear what "ag" means.
  - B) There are no separate descriptions of Figures 8-10.
  - C) The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. The hyperlinks are present on page 43, lines 4 and 5.

Appropriate correction is required. No new matter should be introduced.

### ***Claim Rejections - 35 USC § 112***

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 1 is indefinite over the recitation of "essentially complementary" (line 5). It is not clear what is encompassed by this term. On page 26 of the specification (first paragraph) Applicants state "Hence essentially complementary often means that more than 90% of the bases of the nucleic acid or sequence in question can form base pairs with the certain nucleic acid or sequence under stringent conditions.". However, Applicants do not define what hybridization conditions are considered "stringent".

B) Claim 1 is indefinite over the recitation of "... a probe having a binding sequence D which can bind to a sequence B... or to the complement thereof..." (emphasis added). According to Figure 1, complement of sequence B is sequence B', so if sequence D binds to sequence B, it would not bind to sequence B'.

C) Claim 3 is indefinite over the recitation of "... at least one of the primers has nucleotides ... which do not hybridize directly with the nucleic acid to be detected..." (emphasis added). It is not clear what it means for a nucleotide to hybridize directly with a sequence, and Applicants did not define what "direct hybridization" means.

D) Claim 4 is indefinite over the recitation of "...at least one of the binding sequences is not specific for the nucleic acid to be detected". It is not clear what is encompassed by the term "not specific". On page 42, first paragraph, Applicants state "A sequence is specific in the sense of the invention when, as a result of a consecutive sequence of nucleobases, it would in principle be able to bind under stringent conditions only to one sequence on the nucleic acid to be detected but not to

nucleic acids of other organisms or species or groups of organisms that are not to be detected.”.

However, Applicants do not define what hybridization conditions are considered “stringent”.

E) Claim 4 is indefinite over the recitation of “... at least one of the binding sequences is not specific for the nucleic acid to be detected”, as applied to sequences A and C. Claim 1, from which claim 4 depends, lists the following binding sequences: A and C’, which are part of the nucleic acid to be detected, and a binding sequence D, which is a probe binding to sequence B. It is not clear how a sequence which is a part of the target nucleic acid (sequence A and C’) can be non-specific.

F) Claim 11 is indefinite over the recitation of “...at least one of the primers is not specific for the nucleic acid to be detected”. It is not clear what is encompassed by the term “not specific”. On page 42, first paragraph, Applicants state “A sequence is specific in the sense of the invention when, as a result of a consecutive sequence of nucleobases, it would in principle be able to bind under stringent conditions only to one sequence on the nucleic acid to be detected but not to nucleic acids of other organisms or species or groups of organisms that are not to be detected.”. However, Applicants do not define what hybridization conditions are considered “stringent”.

G) Claim 12 is indefinite over the recitation of “...two of the primers are not specific for the nucleic acid to be detected”. It is not clear what is encompassed by the term “not specific”. On page 42, first paragraph, Applicants state “A sequence is specific in the sense of the invention when, as a result of a consecutive sequence of nucleobases, it would in principle be able to bind under stringent conditions only to one sequence on the nucleic acid to be detected but not to nucleic acids of other organisms or species or groups of organisms that are not to be detected.”. However, Applicants do not define what hybridization conditions are considered “stringent”.

H) Claim 13 is indefinite over the recitation of “...the probe is not specific for the nucleic acid to be detected”. It is not clear what is encompassed by the term “not specific”. On page 42,

first paragraph, Applicants state "A sequence is specific in the sense of the invention when, as a result of a consecutive sequence of nucleobases, it would in principle be able to bind under stringent conditions only to one sequence on the nucleic acid to be detected but not to nucleic acids of other organisms or species or groups of organisms that are not to be detected.". However, Applicants do not define what hybridization conditions are considered "stringent".

***Claim Rejections - 35 USC § 102***

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 2, 3, 5-7, 10 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Whitby et al. (J. Virol. Methods, vol. 51, p. 75-88, 1995).

Regarding claim 1, Whitby et al. teach amplification hepatitis C virus (HCV) cDNA using primers which amplify the 5' non-coding region of HCV and detection of the amplified fragments (= amplificates) with probes . The primers were PT1-PT4. Sense primers PT1 and PT4 were located between base pairs 90-109 and 100-109, respectively, whereas the antisense primers PT2 and PT4 were located between base pairs 153-171 and 140-153, respectively. The detection probes were located between base pairs 123 and 142 (Abstract; page 76, paragraphs 3 and 4, continued on page 77; Table 1).

Therefore, the following amplification products were created:

<u>Primer combination</u>	<u>PCR product length, bp</u>
PT1-PT2	82
PT1-PT4	70

PT3-PT2	72
PT3-PT4	60

Therefore all of the amplification products were less than 100 bp long.

Regarding claim 2, Whitby et al. teach the probes overlapping with the primer PT4 (Table 1).

Regarding claim 3, Whitby et al. teach a modified PT3 primer which contains a recognition sequence for the DNA-binding GCN4 protein (Table 1).

Regarding claim 5, Whitby et al. teach three amplification products which are shorter than 74 bp (see above; Fig. 1).

Regarding claim 6, Whitby et al. teach primers PT3BIO, labeled with biotin, and PT4 DNP, labeled with dinitrophenol (DNP), to facilitate immobilization of the amplification products on a solid support (Table 1; page 78, paragraph 2.3). Whitby et al. also teach detectably-labeled probes INT1BIO, INT1DNP, INT1XO and INT1AP, which are labeled with biotin, DNP, xanthine oxidase and alkaline phosphatase, respectively (Table 1; page 78, 79, paragraph 2.4).

Regarding claim 7, Whitby et al. teaches primers labeled with biotin, DNP and a GCN4 recognition sequence (Table 1). Whitby et al. also teach probe INT2BIO, labeled with biotin and immobilized on a solid support, for capture of DNP-labeled amplification products (Table 1, page 78, paragraph 2.3).

Regarding claim 10, Whitby et al. teach detection of the amplification products by chemiluminescence (Table 2; pages 78 and 79, paragraph 2.4).

Regarding claim 14, Whitby et al. teach amplification buffer containing 200 µM of each dNTP. Therefore Whitby et al. do not explicitly teach nucleotides complementary to A, G, C or T, but the presence of all four nucleotides is inherent in the conditions for amplification.

***Claim Rejections - 35 USC § 103***

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Whitby et al. as applied to claim 1 above, and further in view of Livak et al. (U. S. Patent No. 5,538,848; cited in the IDS).

A) Claim 8 is drawn to a probe labeled with a fluorescence quencher and a fluorescent dye.

B) Teachings of Whitby et al. are described above. Whitby et al. teach labeled probes, but do not teach a probe labeled with a fluorescence quencher and a fluorescent dye.

C) Livak et al. teach a probe labeled with a reporter molecule (= fluorescent dye) and a quencher, the probe being used for monitoring of the progress of amplification reaction (Abstract; Figure 1; col. 3, lines 29-56; col. 5, lines 38-58).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the reporter-quencher labeled probe of Livak et al. in the HCV detection method of Whitby et al. The motivation to do so, provided by Whitby et al., would have been that real-time quantitation of nucleic acid amplification was achieved using such probe, and real-time monitoring of amplification prevented cross-contamination of samples, especially important in diagnostic applications (col. 1, lines 22-52; col. 3, lines 8-12).

11. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Whitby et al. as applied to claim 1 above, and further in view of Wittwer (U. S. Patent No. 6,245,514 B1).

A) Claim 9 is drawn to one of the primers labeled with a first energy transfer component and a probe labeled with a second energy transfer component which is different from the first energy transfer component.

B) Teachings of Whitby et al. are described above. Whitby et al. teach labeled primers and probes, but do not teach one of the primers labeled with a first energy transfer component and a probe labeled with a second energy transfer component which is different from the first energy transfer component.

C) Wittwer teaches fluorescence energy transfer pairs for detecting the presence of target analyte. Wittwer teaches detection of PCR products by resonance energy transfer between one labeled primer and one labeled probe which hybridizes between the PCR primers. Exemplary energy transfer pair can comprise fluorescein as a donor and Cy5 or Cy5.5 as the acceptor (col. 3, lines 66, 67; col. 4, lines 1-3; col. 5, lines 63-67; col. 6, lines 1-13, 54, 55; col. 7, lines 31-52; col. 31, lines 35-67; col. 32, lines 1-63).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the donor-acceptor energy transfer between a primer and a probe of Wittwer in the HCV detection method of Whitby et al. The motivation to do so, provided by Wittwer, would have been that using labeled probe and primer provided "a superior monitor of product accumulation for quantitation" and resulted in more precise measurement of fluorescence intensity than other methods (col. 32, lines 6-18 and 59-63).

12. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Whitby et al. as applied to claim 1 above, and further in view of Koster (WO 96/29431, cited in the IDS).

A) Claim 15 is drawn to the detection of amplificates by mass spectroscopy.

B) Teachings of Whitby et al. are described above. Whitby et al. do not teach detection of amplificates by mass spectroscopy.

C) Koster teaches detection of nucleic acids by mass spectrometry. Koster teaches detection of an amplified target nucleic acid (= amplificate) by immobilization of the target nucleic acid on a solid support and detection of the target by mass spectrometry. Immobilization of the target can be achieved by hybridizing the target with a capture probe which has been immobilized on solid support (page 4, lines 15-38; page 5, lines 1-11; Figure 1A; Figure 4; page 15, lines 34-39; page 16, lines 1-28). Mass spectrometry was used to detect a 67 bp amplification product from hepatitis B virus (HBV) (page 27, lines 24-39; page 28-30).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used mass spectrometry detection of PCR products of Koster in the HCV detection method of Whitby et al. The motivation to do so, provided by Koster, would have been that mass spectrometry provided high detection sensitivity and accuracy of mass, i.e., molecular weight, determination (page 2, lines 33-37).

13. No references were found teaching or suggesting claims 4, 11-13, but they are rejected for reasons given above.

### ***Conclusion***

14. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Tavernarakis et al., WO 94/03635.

B) Sninsky et al., EP 0 229 701 A2 (cited in the IDS).

C) Resnick et al., EP 0 787 807 A2.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (703) 306-5877. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

March 24, 2003

Teresa Strzelecka, Ph. D.

Patent Examiner